cancer tissues and have developed monoclonal antibodies to detect [−2]pPSA and other isoforms of pPSA for Western blot analysis. PSA was immunoaffinity purified from 100–200 mL of serum from five men with biopsy-proven prostate cancer (PSA range: 6–24 ng/mL; mean: 13.4 ng/mL) and three biopsy-negative patients (PSA range: 7–12 ng/mL; mean: 9.7 ng/mL). The truncated [−2]pPSA was found to range from 25% to 95% of the free PSA in the five cancer samples; however, in the three biopsy-negative samples, this value was only 6%–19%. Immunohistochemical studies showed positive staining for [−2]pPSA in prostate cancer tissue epithelium and that [−2]pPSA was enriched in cancer cell secretions, thereby further strengthening the view that [−2]pPSA is naturally present in prostate tissues and is not the artifactual result of tissue extraction methodologies. The authors also performed in vitro activation studies, which revealed that hK2 and trypsin readily activated full-length pPSA by release of the pro-leader peptide but were unable to activate [−2]pPSA to mature PSA. Hence, once formed, [−2]pPSA appears to be a stable but inactive isoform of PSA. From this work, the authors have concluded that truncated [−2]pPSA may represent an important new diagnostic marker for the early detection of prostate cancer. The authors also reported preliminary results of an unpublished study that serum [−2]pPSA levels were threefold higher in 20 biopsy-positive patients compared to 20 biopsy-negative patients with total serum PSA levels between 2 and 22 ng/mL.

The investigations reviewed here are promising and may lead to the development of pPSA as a new marker for the early detection of prostate cancer. Clinical studies with much larger patient population are required, however. In addition, as free PSA constitutes only a small percentage of total PSA, at present, large volumes of serum are required to obtain pPSA information. This may negatively impact pPSA as a potential new marker. Further knowledge of the role of [−2]pPSA will enable us to perform comprehensive trials of pPSA in prostate cancer early detection. ■

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Urologic Oncology

Testicular Microlithiasis, Chemotherapy for Stage I Seminoma, and Chemotherapy for Advanced Extragonadal Germ Cell Tumors

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[*Rev Urol.* 2002;4(4):200–202]

Previous reports have indicated that testicular microlithiasis may be associated with testicular cancer.[1,2] Some physicians have recommended follow-up with scrotal ultrasound and physical examination every 6–12 months.[1,2] However, many of these publications fail to distinguish between patients with only microlithiasis (isolated microlithiasis) and patients with associated sonographic abnormalities.

Testicular Microlithiasis: What Is Its Association with Testicular Cancer?

Bach AM, Hann LE, Hadar O, et al.
Radiology. 2001;220:70–75.

In a recent publication, Bach and colleagues retrospectively reviewed the scrotal sonograms of 528 men with a mean age of 45 years (reason for referral was not mentioned but was presumably for genitourinary symptoms or abnormal examination). Of the 48 patients with microlithiasis, 13 (27%) had testicular cancer. The authors concluded that intratesticular microlithiasis is highly associated with the presence of a testicular mass and testicular

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cancer. However, closer inspection of the data reveals that testicular cancer was present in 52% of patients with a sonographic testicular mass and microlithiasis, but in only 4% of patients with microlithiasis alone. These data suggest that isolated testicular microlithiasis is rarely associated with cancer.

The Prevalence of Testicular Microlithiasis in an Asymptomatic Population of Men 18–35 Years Old.

Peterson AC, Bauman JM, Light DE, et al.
J Urol. 2001;166:2061–2064.

Peterson and colleagues prospectively evaluated 1504 asymptomatic healthy men (mean age 22.4 years) attending the Army Reserve Officer Training Corps training camp. Of these subjects, 5.6% had microlithiasis on sonography and all had normal α-fetoprotein (AFP) and β-human chorionic gonadotropin (B-HCG) levels. Only 1 patient with microlithiasis had testicular cancer (apparently identified as a mass on sonography). Because these reports did not follow patients with microlithiasis, they do not provide information on the risk of subsequently developing cancer. A few case reports describe patients with testicular microlithiasis that developed germ cell tumors from 10 months to 11 years later.[1] However, comprehensive follow-up data on patients with microlithiasis is lacking.

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Currently there is no convincing evidence that testicular microlithiasis is premalignant or associated with an increased risk of developing cancer. Furthermore, when microlithiasis is the only testicular abnormality (isolated microlithiasis), associated cancer is rare. A small number of patients with microlithiasis may subsequently develop cancer; however, it is unclear if microlithiasis increases the risk of malignancy. In newly diagnosed patients with isolated microlithiasis, some recommend high-resolution sonography and serum markers (AFP and B-HCG) to search more thoroughly for associated neoplasm; however, current data does not justify testis biopsy or orchiectomy.[2]

How should patients with isolated microlithiases be followed up? Some authors recommend testicular sonography[1,2] and serum tumor markers[2] at least annually. Patients with a history of cryptorchidism are at risk for testicular malignancy; however, these patients are usually followed with physical examination, not with serial ultrasound and tumor markers. Why not follow patients with testicular microlithiasis in the same fashion? Unfortunately there is not enough data to make strong recommendations. Patients with microlithiasis should be advised of a possible association between microlithiases and malignancy and should perform periodic self-examination. Physical examination by a physician should probably be done at least once a year. Periodic scrotal ultrasound may be prudent. However, sonogram should definitely be performed if scrotal exam changes or symptoms develop.

Twelve-Year Experience with Two Courses of Adjuvant Single-Agent Carboplatin Therapy for Clinical Stage I Seminoma.

Reiter WJ, Brodowicz T, Alavi S, et al.
J Clin Oncol. 2001;19(1):101–104.

Seventy percent to 80% of all seminoma patients are classified as clinical stage I. Traditional treatment for these patients has consisted of radical inguinal orchiectomy followed by 28 to 30 Gy of radiation therapy to the retroperitoneum, including the ipsilateral iliac lymph nodes.[3] Although survival and cure rates remain in excess of 90%, toxicities associated with radiation therapy include peptic ulcer disease and secondary malignancies. As a result of these morbidities, recent studies have investigated the roles of surveillance therapy and adjuvant chemotherapy.

In a retrospective analysis, Reiter and colleagues investigated the effects of two cycles of outpatient carboplatin on 107 patients with clinical stage I seminoma. Compared to cisplatin, carboplatin does not cause nephrotoxicity, neuropathy, or ototoxicity. Side effects of carboplatin include nausea and myelosuppression, most notably thrombocytopenia.

A total of 107 patients received 400 mg/m^2 of carboplatin (dissolved in 500 ml saline) within 10 days of orchiectomy; 43 patients received the second course 28 days later, and the remaining 64 patients received the second course on day 21 (at a different institution). Patients were then followed every 3 months for the first 2 years, every 6 months from years 2 to 5, and then annually after that. Median follow-up in the study was 74 months.

During the study, 6 patients died of unrelated causes (4 with myocardial infarction, 1 from a car accident, and 1 from metastatic rectal cancer). The remaining 101 patients were alive without evidence of disease. Toxicity was limited to nausea (31%) and vomiting (14%) in patients who were given antiemetics at the time of carboplatin adminis-

tration. Hematologic toxicities consisted of leukopenia (10.7% World Health Organization grade 1 and 2.1% grade 2). There were no reported cases of nephrotoxicity, neurotoxicity, ototoxicity, anemia, or thrombocytopenia.

The results of this study support recent data that two courses of carboplatin are necessary when considering adjuvant chemotherapy for clinical stage I seminoma. The authors cited studies that included recurrence rates as high as 9% in regimens using only one course of carboplatin.[4]

The third treatment option for clinical stage I seminoma is surveillance. However, 20%–25% of patients on surveillance eventually relapse, adding psychological stress to patients already diagnosed with cancer. Furthermore, diligent patient compliance with follow-up is necessary.

Radiation therapy for clinical stage I seminoma remains the standard of care to which adjuvant chemotherapy regimens must be compared. Delayed complications such as ulcer and secondary malignancies related to radiation have lead to the emergence of adjuvant therapy trials. Phase III trials comparing the efficacy of carboplatin and radiation therapy in these patient cohorts have been initiated by the German Testicular Cancer Study Group and the English Medical Research Council.[5]

Second-Line Chemotherapy in Patients with Relapsed Extragonadal Nonseminomatous Germ Cell Tumors: Results of an International Multicenter Analysis.

Hartmann JT, Einhorn L, Nichols CR, et al.
J Clin Oncol. 2001;19(6):1641–1648.

Primary extragonadal germ cell tumors are rare, but relapses have generally been treated with chemotherapy regimens similar to those used in metastatic testicular cancer. In cases of metastatic testicular cancer, salvage chemotherapy still offers chances for cure, but the results for patients with relapsed extragonadal germ cell tumors are still uncertain. Clinical differences between gonadal and extragonadal tumors suggest that they may be biologically distinct. A retrospective study of 142 patients treated between 1975 and 1996 at 11 European and American centers was conducted to determine prognostic indicators of therapeutic efficacy of salvage chemotherapy in patients with nonseminomatous extragonadal germ cell tumors. Median follow-up was 11 months and median age was 29 years.

Of these patients, 79 (56%) had primary mediastinal tumors and 61 (43%) had primary retroperitoneal tumors. The remaining two patients showed widespread pulmonary, mediastinal, and retroperitoneal involvement. All patients either relapsed after or during primary cisplatin-based chemotherapy, but 44 patients initially had complete response (CR) to induction therapy.

Salvage regimens included ifosfamide, vinblastine, paclitaxel, or high-dose therapy based on carboplatin and etoposide; 43 (30%) patients received a combination of cisplatin and ifosfamide, 29 (20%) received cisplatin with etoposide or vinblastine, and 48 (33%) received carboplatin and etoposide with ifosfamide or cyclophosphamide followed by autologous bone marrow transplantation. The remaining patients received single-agent therapy.

Univariate statistical analyses showed that primary mediastinal tumor location, lack of response to cisplatin induction therapy, elevated β-hCG, and normal LDH at initial diagnosis were negative prognostic factors for survival. Extent of disease, location of relapse, sites of visceral metastases, and type of salvage treatment did not significantly influence survival.

Using multivariate analyses, both primary mediastinal location and lack of response to cisplatin were found to be independent negative factors with a twofold increased hazard ratio for death. Median survival for patients with either of these two factors was 6–10 months compared to 21 months for patients with primary tumors originally located in the retroperitoneum.

Overall, the long-term survival of patients with primary retroperitoneal extragonadal tumors was 30%, whereas patients with primary tumors in the mediastinum had long-term survival rates that were less than 10%. In comparison, survival rates for patients undergoing salvage chemotherapy for recurrent/metastatic testicular cancer range from 20% to 50%.[3] The authors concluded that the therapeutic advances of second-line therapy in patients with advanced testicular cancer do not lead to similar survival rates in patients with extragonadal germ cell tumors. New strategies are needed, especially for patients with primary mediastinal tumors and for patients who do not respond to induction therapy with cisplatin. ■

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